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THE WEINBERG GROUP INC.

WASHINGTON
NEW YORK
SAN FRANCISCO
BRUSSELS
PARIS

DEC 17 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

SUITABILITY PETITION

This petition is submitted pursuant to 21 CFR parts 10.20 and 10.30, as provided for in 21 CFR 314.93, and Section 505(j)(2)(c) of the Federal Food, Drug and Cosmetic Act to request the Commissioner of the Food and Drug Administration to declare that the drug product Cefadroxil Hemihydrate Dispersible Tablets, 125 mg, 250 mg and 500 mg, are suitable for submission as an abbreviated new drug application (ANDA).

A. Action Requested

The petition is submitted for a change in dosage form of the drug product from "powder for oral suspension" and "capsules" to "dispersible tablets". The listed drug product is Duricef® for oral suspension 125 mg/5 mL, 250 mg/5 mL and 500 mg/5 mL and also Duricef® Capsules 500 mg manufactured by Bristol Myers Squibb Company. Cefadroxil will be marketed as dispersible tablets in dosage strengths of 125 mg, 250 mg and 500 mg. The drug, the route of administration and the recommendations for use are the same as the listed drug product. The proposed product would differ only in dosage form from Bristol Myers Squibb's marketed product.

The proposed drug product is expected to demonstrate bioequivalence to 500 mg/5ml suspension and 500 mg capsule dosage forms of the listed product, which will be submitted at a later date.

B. Statement of Grounds

Dispersible tablet is presented for administration by dispersing a single tablet in a specified amount of water.

The new dosage form would be a better alternative to the powder for oral suspension with regards to the following advantages:

Unit dose dispensing.
Convenience to the patient with respect to the administration during traveling.
Storage of the product will not require special condition like refrigeration.

99P-5449

CP 1

Better precision of dosage over the traditional teaspoonful.
Ease of carrying.

Additionally, the 500 mg dispersible tablets can also be a viable alternative to the capsule dosage form for geriatric patients who have problems swallowing the solid oral dosage forms.

As the proposed product will differ only in dosage form, and the indications, strength, route of administration, intended patient population and recommendations for use remain the same as Bristol Myers Squibb's marketed product, therefore there will be no difference in the safety and efficacy of the proposed dispersible tablets.

A package insert of Bristol Myers Squibb's Duricef® is attached along with the draft package insert of the proposed Cefadroxil Dispersible Tablets.

C. Pediatric Use Information

As the package insert of Bristol Myers Squibb's Duricef® for oral suspension contains adequate dosing and administration information for the pediatric population, no additional studies are required.

D. Environmental Impact

An environmental assessment report on the action requested in this petition is not required under 2 1 CFR 25.24.

E. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

F. Certification

The undersigned certifies that to the best of its knowledge, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Sincerely,

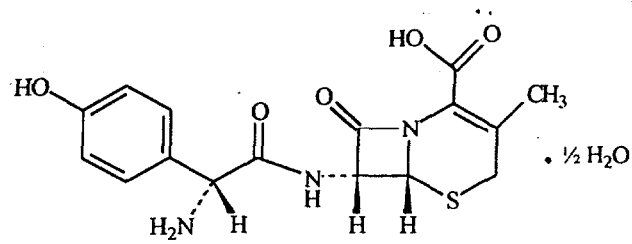
Nicholas M. Fleischer, R.Ph., Ph.D.
Director of Biopharmaceutics
THE WEINBERG GROUP INC.

CEFADROXIL DISPERSIBLE TABLETS

Rx only

DESCRIPTION

Cefadroxil USP (hemihydrate) is a semisynthetic cephalosporin antibiotic intended for oral administration. It is white to off- white crystalline powder. It is slightly soluble in water and it is acid-stable. It is chemically designated as 5-Thia- 1- azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 7-[[amino (4-hydroxyphenyl) acetyl] amino]-3-methyl-8-oxo-, hemihydrate, [6R-[6α, 7β (R*)]]-. It has the formula $C_{16}H_{17}N_3O_5S \cdot 1/2\ H_2O$ and the molecular weight of 372.39. It has the following structural formula:



Each dispersible tablet for oral administration contains Cefadroxil hemihdyrate equivalent to 125 mg, 250 mg or 500 mg cefadroxil.

The inactive ingredients will be furnished when ANDA is submitted, since this is proprietary information. The inactives are GRAS ingredients at the appropriate levels.

CLINICAL PHARMACOLOGY

Cefadroxil is rapidly absorbed after oral administration. Following single doses of 500 and 1000 mg, average peak serum concentrations were approximately 16 and 28 mcg/mL, respectively . Measurable levels were present 12 hours after administration. Over 90% of the drug is excreted unchanged in the urine within 24 hours. Peak urine concentrations are approximately 1800 mcg/mL during the period following a single 500-mg dose. Increases in dosage generally produce a proportionate increase in cefadroxil urinary concentration. The urine antibiotic concentration, following a 1-g dose, was maintained well above the MIC of susceptible urinary pathogens for 20 to 22 hours.

Microbiology

In vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cefadroxil has been shown to be active against following organisms both *in* vitro and in clinical infections (see INDICATIONS AND USAGE):

Beta-hemolytic streptococci
Staphylococci, including penicillinase-producing strains
Streptococcus (Diplococcus) pneumoniae
Escherichia coli
Proteus mirabiiis
Klebsiella species
Moraxella (Branhamella) catarrhalis

Note: Most strains *of Enterococcus faecalis (formerly Streptococcus faecalis)* and *Enterococcus faecium* (formerly *Streptococcus faecium)* are resistant to cefadroxil. It is not active against most strains *of Enterobacter* species, *Morganella morganii* (formerly *Proteus morganii),* and *P. vulgaris.* It has no activity against *Pseudomonas* species and *Acinetobacter calcoaceticus* (formerly *Mima and Herella* species).

Susceptibility tests : Diffusion techniques

The use of antibiotic disk susceptibility test methods which measure zone diameter give an accurate estimation of antibiotic susceptibility. One such standard procedure[1] which has been recommended for use with disks to test susceptibility of organisms to cefadroxil uses the cephalosporin class (cephalothin) disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefadroxil.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30 mcg cephalothin disk should be interpreted according to the following criteria :

Zone Diameter (mm)	Interpretation
≥ 18	(S) Susceptible
15 - 17	(I) Intermediate
≤ 14	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by *generally* achievable blood levels. A report of "Intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (eg, urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30 mcg cephalothin disk should give the following zone diameters :

Organism	Zone Diameter (mm)
Staphylococcus aureus ATCC 25923	*29 - 37*
Escherichia coli ATCC 25922	*17-22*

Dilution Techniques

When using the NCCLS agar dilution or broth dilution (including microdilution) method[2] or equivalent, a bacterial isolate may be considered susceptible if the MIC (minimum inhibitory concentration) value for cephalothin is 8 mcg/mL or less. Organisms are considered resistant if the MIC is 32 mcg/mL or greater. Organisms with an MIC value of less than 32 mcg/mL but greater than 8 mcg/mL are intermediate.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cephalothin powder should give MIC values in the range of 0.12 mcg/mL and 0.5mcg /mL for *Staphylococcus aureus* ATCC 29213. For *Escherichia coli* ATCC 25922, the MIC range should be between 4.0 mcg/mL and 16.0 mcg/mL. For *Streptococcus faecalis* ATCC 29212, the MIC range should be between 8.0 and 32.0 mcg/mL.

INDICATIONS AND USAGE

Cefadroxil is indicated for the treatment of patients with infection caused by susceptible strains of the designated organisms in the following diseases :

Urinary tract infections caused by *E. coli, P.mirabilis,* and *Klebsiella* species.

Skin and skin structure infections caused by staphylococci and/or streptococci.

Pharyngitis and/or tonsillitis caused by Streptococcus pyogenes (Group A beta-hemolytic Streptococci).

Note: Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Cefadroxil is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of cefadroxil for the prophylaxis of subsequent rheumatic fever are not available.

Note: Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Cefadroxil is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE THERAPY WITH CEFADROXIL IS INSTITUTED. CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFADROXIL. CEPHALOSPORINS. PENICILLINS OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS. CAUTION SHOULD BE EXERCISED BECAUSE CROSS-SENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY.

IF AN ALLERGIC REACTION TO CEFADROXIL OCCURS. DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES. INCLUDING OXYGEN.

INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with all antibacterial agents, including cefadroxil, and may range from mild to life-threatening. Therefore, it is important to consider this. diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis"

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug effective against *Clostridium difficile*.

PRECAUTIONS

General

Cefadroxil should be used with caution in the presence of markedly impaired renal function (creatinine clearance rate of less than 50 mL/min/1.73 M^2) (See DOSAGE AND ADMINISTRATION). In patients with known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy.

Prolonged use of cefadroxil may result in the overgrowth of nonsusceptible organisms. Careful observation of the patients is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefadroxil should be prescribed with caution in individuals with history of gastrointestinal disease particularly colitis.

Drug/Laboratory Test Interactions

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term studies have been performed to determine carcinogenic potential. No genetic toxicity tests have been performed.

Pregnancy : Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 11 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefadroxil. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Cefadroxil has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: Caution should be exercised when cefadroxil is administered to a nursing mother.
Pediatric Use: (See DOSAGE AND ADMINISTRATION)

ADVERSE REACTIONS

Gastrointestinal

Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (See WARNINGS). Dyspepsia, nausea and vomiting have been reported rarely. Diarrhea has also occurred.

Hypersensitivity

Allergies (in the form of rash, urticaria, angioedema, and pruritus) have been observed. These reactions usually subsided upon discontinuation of the drug. Anaphylaxis has also been reported.

Other

Other reactions have included genital pruritus, genital moniliasis, vaginitis, moderate transient neutropenia, fever, and minor elevations in serum transaminase. Agranulocytosis, thrombocytopenia, erythema multiforme, Stevens-Johnson syndrome, serum sickness, and arthralgia have been rarely reported.

In addition to the adverse reactions listed above which have been observed in patients treated with cefadroxil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics :

Toxic epidermal necrolysis, abdominal pain, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, prolonged prothrombin time, positive Coombs test, increased BUN, increased creatinine, elevated alkaline phosphatase, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), elevated bilirubin, elevated LDH, eosinophilia, pancytopenia, neutropenia.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

OVERDOSAGE

A study of children under six years of age suggested that ingestion of less than 250 mg/kg of cephalosporins is not associated with significant outcomes. No action is required other than general support and observation. For amounts greater than 250 mg/kg, induce gastric emptying. In five anuric patients, it was demonstrated that an average of 63% of a 1 g oral dose is extracted from the body during a 6-8 hour hemodialysis session.

DOSAGE AND ADMINISTRATION

Cefadroxil is acid-stable and may be administered orally without regard to meals. Administration with food may be helpful in diminishing potential gastrointestinal complaints ocassionally associated with oral cephalosporin therapy.

Adults

Urinary Tract Infections : For uncomplicated lower urinary tract infections (i.e. cystitis) the usual dosage is 1 or 2 g per day in single (q.d.) or divided doses (b.i.d).
For all other urinary tract infections the usual dosage is 2 g per day in divided doses (b.i.d).
Skin and Skin Structure Infections : For skin and skin structure infections the usual dosage is 1 g per day in single (q.d.) or divided doses (b.i.d).
Pharyngitis and Tonsillitis : Treatment of group A beta-hemolytic streptococcal pharyngitis and tonsillitis - 1 g per day in single (q.d.) or divided doses (b.i.d) for 10 days.

Children

For urinary tract infections, the recommended daily dosage for children is 30 mg/kg/day in divided doses every 12 hours. For pharyngitis, tonsillitis, and impetigo, the recommended daily dosage for children is 30 mg/kg/day in a single dose or in equally divided doses every 12 hours. For other skin and skin structure infections, the recommended daily dosage is 30 mg/kg/day in equally divided doses every 12 hours. In the treatment of beta-hemolytic streptococcal infections; a therapeutic dosage of cefadroxil should be administered for at least 10 days.

See chart for toal daily dosage for children.

DAILY DOSAGE OF CEFADROXIL DISPERSIBLE TABLETS				
Child's weight		125 mg	250 mg	500 mg
lbs	kg			
10	4.5	1 tab.		
20'	9.1	2 tabs.	1 tab.	
30	13.6	3 tabs.	1 1/2 tabs	
40	18.2	4 tabs.	2 tabs.	1 tab.
50	22.7	5 tabs.	2 1/2 tabs.	
60	27.3	6 tabs.	3 tabs.	1 1/2 tabs.
70 & above	31.8+			2 tabs.

In patients with renal impairment, the dosage of cefadroxil should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1000 mg of cefadroxil and the maintenance dose (based on the creatinine clearance rate [mL/min/1.73 M^2]) is 500 mg at the time intervals listed below .

Creatinine Clearances	Dosage Interval
0-10 mL/min	36 hours
10-25 mL/min	24 hours
25-50 mL/min	12 hours

Patients with creatinine clearance rates over 50 mL/min may be treated as if they were patients having normal renal function.

Cefadroxil Dispersible Tablets should be dispersed in one teaspoonful of water before administration.

HOW SUPPLIED

Cefadroxil Dispersible Tablets 125 mg, 250 mg and 500 mg
Packaging size to be determined.

REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard, *Performance Standards for Antimicrobial Disk Susceptibility Test*, 4th Edition, Vol. 10(7):M2-A4, Villanova, PA, April, 1990.

2. National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 2nd Edition, Vol. 10(8): M7-A2, Villanova, PA, April, 1990.

November 1999

hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Central Nervous System-Dizziness or fatigue has been reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior have each been reported in approximately 6 of 1000 patients.

Respiratory—Bronchospasm has been reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS).

Gastrointestinal—Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence have been reported in 1 to 5 of 1000 patients.

Miscellaneous—Each of the following has been reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Reversible alopecia has been reported infrequently.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established.

Central Nervous System—Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability with slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal—Mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes.

Hematologic—Agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura.

Allergic—Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Miscellaneous—Pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with nadolol.

Bendroflumethiazide

Gastrointestinal—Nausea, vomiting, cramping and anorexia are not uncommon; diarrhea, constipation, gastric irritation, abdominal bleeding, jaundice (intrahepatic cholestatic jaundice), hepatitis, and sialadenitis occasionally occur; and pancreatitis has been reported.

Central Nervous System—Dizziness, vertigo, paresthesia, headache, and xanthopsia occasionally occur.

Hematologic—Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, and aplastic anemia have been reported.

Dermatologic-Hypersensitivity—Purpura, exfoliative dermatitis, pruritus, ecchymosis, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), respiratory distress including penumonitis, fever, and anaphylactic reactions occasionally occur; photosensitivity and rash have been reported.

Cardiovascular—Orthostatic hypotension may occur and may be potentiated by coadministration with certain other drugs (e.g., alcohol, barbiturates, narcotics, other antihypertensive medications, etc.; see PRECAUTIONS, Drug Interactions).

Other—Muscle spasm, weakness, or restlessness is not uncommon; hyperglycemia, glycosuria, metabolic acidosis in diabetic patients, hyperuricemia, allergic glomerulonephritis, and transient blurred vision occassionally occur.

whenever adverse reactions are moderate or severe, thiaside dosage should be reduced or therapy withdrawn.

OVERDOSAGE.

In the event of overdosage, nadolol may cause excessive bradycardia, cardiac failure, hypotension, or bronchospasm. In addition to the expected diuresis, overdosage of bendroflumethiazide may produce varying degrees of lethargy which may progress to coma with minimal depression of respiration and cardiovascular function and without significant serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown. Gastrointestinal irritation may occur. Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function.

Treatment

Nadolol can be removed from the general circulation by hemodialysis. In determining the duration of corrective therapy, note must be taken of the long duration of the effect of nadolol. In addition to gastric lavage, the following measures should be employed, as appropriate.

Excessive Bradycardia—Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure—Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension—Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm-Administer a β_2-stimulating agent and/or a theophylline derivative.

Stupor or **Coma**—Supportive therapy as warranted.

Gastrointestinal **Effects**—Syptomatic treatment as needed

BUN **and/or** Serum **Electrolyte Abnormalities**—Institute supportive measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED (SEE INDICATIONS). CORZIDE MAY BE ADMINISTERED WITHOUT REGARD TO MEALS.

Bendroflumethiazide is usually given at a doss of 5 mg daily. The usual initial dose of nadolol is 40 mg once daily whether used alone or in combination with a diuretic. Bendroflumethiazide in CORZIDE is 50 percent more bioavailable than that of 5 mg Naturetin tablets. Conversion from 5 mg NATURETIN to CORZIDE represents a 30 percent increase in dose of bendroflumethiazide.

The initial dose of CORZIDE (Nadolol and Bendroflumethiazide Tablets) may therefore be the 40 mg/5 mg tablet once daily. When the antihypertensive response is not satisfactory, the dose may be increased by administering the 80 mg/5 mg tablet once daily.

When necessary, another hypertensive agent may be added gradually beginning with 50 percent of the usual recommended starting dose to avoid an excessive fall in blood pressure.

Dosage Adjustment in Renal Failure—Absorbed nadolol is excreted principally by the kidneys and, although nonrenal elimination does occur, dosage adjustments are necessary in patients with renal impairment. The following dose intervals are recommended:

Creatinine Clearance (mL/min/1.73m^2)	Dosage Interval (hours)
>50	24
31–50	24–36
10–30	24–48
<10	40–60

HOW SUPPLIED

CORZIDE (Nadolol and Bendroflumethiazide Tablets)

- **40 mg nadolol combined with 5 mg bendroflumethiazide** in bottles of 100 tablets (NDC 0003-0283-50).
- **80 mg nadolol combined with 5 mg bendroflumethiazide** in bottles of 100 tablets (NDC 0003-0284-50).

Round, biconvex tablets are white to bluish white with dark blue specks. Each tablet has a full bisect bar. Tablet identification numbers: 40 mg/5 mg combination, 283; 80 mg/5 mg combination, 284.

Storage

Keep bottle tightly closed. Store at room temperature; avoid excessive heat.

BRISTOL LABORATORIES®
A Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
N0545-00 Revised August 1996

DURICEF® ℞

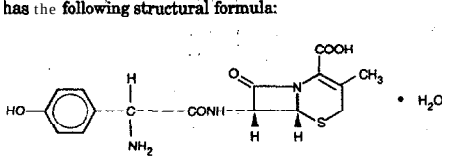
[dur'i-sef]

(cefadroxil monohydrate, USP)

℞ only

DESCRIPTION

DURICEF® (cefadroxil monohydrate, USP) is a semisynthetic cephalosporin antibiotic intended for oral administration. It is a white to yellowish-white crystalline powder. It is soluble in water and it is acid-stable. It is chemically designated as 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[amino(4-hydroxy-phenyl)acetyl] amino]-3-methyl-8-oxo-, monohydrate, [6R-[6α,7β(R*)]]-. It has the formula $C_{16}H_{17}N_3O_6S{\cdot}H_2O$ and the molecular weight of 381.40. It has the following structural formula:



DURICEF film-coated tablets, 1 g, contain the following inactive ingredients: microcrystalline cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glyml, polysorbate 80. simethicone emulsion. and titanium dioxide.

DURICEF for Oral Suspension contains the following inactive ingredients: FD&C Yellow No. 6, flavors (natural and artificial), polysorbate 80, sodium benzoate, sucrose, and xanthan gum.

DURICEF capsules contain the following inactive ingredients: D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40 gelatin. magnesium stearate, and titanium dioxide..

CLINICAL PHARMACOLOGY

DURICEF is rapidly absorbed after oral administration Following single doses of 500 and 1000 mg, average peal serum concentrations were approximately 16 and 28 µg/mL respectively. Measurable levels were present 12 hours after administration. over 30% of the drug-is excreted unchanged in the urine within 24 hours. Peek urine concentrations an approximately 1800 µg/mL during the period following a single 500-mg oral dose. Increases in dosage generally produce a proportionate increase in DURICEF urinary concentration. The urine antibiotic concentration, follow&g a l-g dose. was maintained well above the MIC of susceptible urinary pathogens for 20 to 22 hours.

Microbiology

In vitro tests demonstrate that the cephalosporins am bactericidal because of their inhibition of cell-wall synthesis. Cefadroxil has been shown to be active against the following organisms both in *vitro* and in clinical infections (see INDICATIONS AND USAGE):

Beta-hemolytic streptococci
Staphylococci, including penicillinase-producing s&ids
Streptococcus (Diplococcus) pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Moraxella (Branhamella) catarrhalis.

Note: Most strains of *Enterococcus faecalis* (formerly *Streptococcus faecalis)* and *Enterococcus faecium* (formerly *Streptococcus faecium)* are resistant to DURICEF (cefadroxil monohydrate, USP). It is not active against most strains of *Enterobacter* species, *Morganella morganii* (formerly *Proteus morganii*), and *P. vulgaris*. It has no activity against *Pseudomonas* species and *Acinetobacter calcoaceticus* (formerly *Mima* and *Herellea* species).

Susceptibility tests: Diffusion techniques

The use of antibiotic disk susceptibility test methods which measure zone diameter give an accurate estimation of antibiotic susceptibility. One such standard procedure[1] which has been recommended for use with disks to test susceptibility of organisms to cefadroxil uses the cephalosporin class (cephalothin) disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefadroxil.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 80 µg cephalothin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥18	(S) Susceptible
15–17	(I) Intermediate
a 14	(R) Resistant

A report of 'Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (eg, urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antibiotic am unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. *The 30* µg cephalothin disk should give the *following zone diameters:*

Organism	Zone Diameter (mm)
Staphylococcus aureus ATCC 25923	29–37
Escherichia coli ATCC 25922	17–22

Dilution Techniques

When using the NCCLS agar dilution or broth dilution (including, microdilution) method[2] or equivalent, a bacterial isolate may be considered susceptible if the MIC (minimum inhibitory concentration) value for cephalothin is 8 µg/mL or leas. Organisms are considered resistant if the MIC is 32 µg/mL or greater. Organisms with an MIC value of less than 32 µg/mL but greater than 8 µg/mL am intermediate.

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cephalothin powder should give MIC values in the range of 0.12 µg/mL and 0.5 µg/mL for *Staphylococcus aureus* ATCC 29213. For *Escherichia coli* ATCC 25922, the MIC range should be between 4.0 µg/mL and 16.0 µg/mL. For *Streptococcus faecalis* ATCC 28212, the MIC range should be between 8.0 and 32.0 µg/mL.

INDICATIONS AND USAGE

DURICEF (cefadroxil monohydrate, USP) is indicated for the treatment of patients with infection caused by susceptible strains of the designated organisms in the following diseases:

Urinary tract infections caused by *E. coli*, *P. mirabilis*, and *Klebsiella* species.

Skin and skin structure infections caused by staphylococci and/or streptococci.

Pharyngitis and/or tonsillitis *caused* by *Streptococcus pyogenes* (Group A beta-hemolytic streptococci).

Note: Only penicillin by the intramuscular mute of administration has been shown to be effective in the prophylaxis of rheumatic fever. DURICEF is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of DURICEF far the prophylaxis of subsequent rheumatic fever are not available.

Note: Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

DURICEF (cefadroxil monohydrate, USP) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Continued on next page

Duricef—Cont.

WARNINGS

BEFORE THERAPY WITH DURICEF IS **INSTITUTED, CAREFUL** INQUIRY SHOULD BE MADE TO DETERMINE **WHETHER THE** PATIENT HAS HAD **PREVIOUS** HYPERSENSITIVITY REACTIONS TO **CEFADROXIL, CEPHALOSPORINS,** PENICILLINS, OR **OTHER DRUGS.** IF THIS PRODUCT IS TO BE **GIVEN** TO **PENICILLIN-SENSITIVE** PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE **CROSS-SENSITIVITY** AMONG **BETA-LACTAM** ANTIBIOTICS **HAS**. BEEN CLEARLY DOCUMENTED AND **MAY** OCCUR IN UP TO 16% OF PATIENTS WITH A HISTORY OF PENICILLIN **AL-**LRRGY.

IF AN ALLERGIC **REACTION** TO DURICEF OCCURS, **DISCONTINUE** THE DRUG. SERIOUS **ACUTE HYPER-**SENSITIVITY REACTIONS **MAY** REQUIRE **TREAT-MENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES,** INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS **ANTIHISTAMINES, CORTI-COSTEROIDS, PRESSOR AMINES,** AND AIRWAY **MAN-AGEMENT,** AS **CLINICALLY** INDICATED..

Pseudomembranous colitis has been reported with nearly all a ntibacterial agentsincluding cefadroxil, and may range from mild to **life-threatening. Therefore, it is important** to **consider this diagnosis in patients** who **present with diarrhea subsequent to the administration of antibacterial agents.**

Treatment with antibacterial agents alters the normal flora of the colon and may permit **overgrowth of clostridia.** Studies **indicate that a** toxin **produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."**

After the diagnosis **of pseudomembranous colitis has been established, therapeutic** measures **should be** initiated. Mild **cases** of **pseudomembranous colitis usually respond to discontinuation** of the drug **alone.** In **moderate to severe** cases, **consideration should** be **given to** management with fluids and **electrolytes, protein supplementation and** treatment with **an antibacterial drug effective against *Clostridium difficile*.**

PRECAUTIONS

General

DURICEF should be used with caution in **the presence** of **markedly** impaired **renal** function **(creatinine** clearance rate **of less** than 50 **mL/min/1.73 M²). (See** DOSAGE AND **ADMINISTRATION.) In** patients **with** known **or suspected renal impairment, careful clinical observation** and **appropriate laboratory** studies **should** be made, prior **to** and during therapy.

Prolonged use **of DURICEF** may result in the overgrowth **of nonsusceptible organisms. Careful** observation of the **patient** is **essential.** If **superinfection occurs** during therapy, **appropriate** measures should be taken.

DURICEF® (cefadroxil monohydrate, USP) should be prescribed with **caution** in individuals with history of **gastrointestinal disease, particularly colitis.**

Drug/Laboratory Test **Interactions**

Positive direct **Coombs'** tests have been reported during treatment **with** the **cephalosporin antibiotics.** In **hematologic studies or** in **transfusion cross-matching procedures when antiglobulin tests are performed** on **the** minor **side** or in **Coombs' testing** of newborns **whose** mothers have **received cephalosporin antibiotics** before parturition, **it should** he **recognized** that **a** positive **Coombs' test may be** due to the **drug.**

Carcinogenesis, M&genesis. and **Impairment** of Fertility: **No long-term studies have** been performed **to** determine carcinogenic **potential. No genetic toxicity tests** have been performed.

Pregnancy: 'Pregnancy **Category** B: Reproduction' **studies** have been performed **in** mice and **rats** at doses up **to** 11 times the **human** dose and have revealed **no evidence** of impaired **fertility** or **harm** to the **fetus** due **to** cefadmxil **monohydrate. There are,** however, no adequate and **well** controlled studies **in** pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if **clearly needed.**

Labor and Delivery: DURICEF **(cefadroxil monohydrate, USP)** has not been **studied** for use during labor and d&very Treatment should **only** be **given** if **clearly** needed.

Nursing Mothers: Caution should be exercised when **cefadroxil monohydrate** is administered **to** a nursing mother. Pediatric **Use: (See** DOSAGE AND ADMINISTRATION.)

ADVRRSE REACTIONS

Gastrointestinal

Onset of **pseudomembranous** colitis symptoms may **occur during** or **after** antibiotic treatment **(see** WARNINGS). **Dyspepsia,** nausea and vomiting have been reported rarely. **Diarrhea** has also **occurred.**

Hypersensitivity

Allergies (in the form of rash, **urticaria, angioedema,** and **pruritis)** have been observed. These **reactions** usually **subsided** upon discontinuation of the drug. **Anaphylaxis** has also been reported.

Other

Other reactions have included hepatic dysfunction including **cholestasis** and elevations in **serum transaminase,** genital **pruritus, genital moniliasis,** vaginitis, **moderate transient** neutmpenia, fever. **Agranulocytosis, thrombocytopenia,** idiosyncratic **hepatic** failure, **erythema multiforme, Stevens-Johnson** syndrome, **serum sickness,** and **arthralgia** have been **rarely** reported.

In addition **to** the adverse reactions listed above which have **been** observed in patients treated with **cefadroxil,** the following **adverse reactions and altered laboratory tests have been** reported for **cephalosporin-class antibiotics:**

Toxic epidermal necrolysis, abdominal pain, **superinfection, renal dysfunction, toxic nephropathy, aplastic anemia,** he-m&-tic anemia, **hemorrhage, prolonged prothrombin** time, positive **Coombs' test, increased** BUN, increased **creatinine, elevated alkaline phosphatase, elevated aspartate** amino-**transferase (AST),** elevated **alanine aminotransferase (ALT), elevated bilirubin,** elevated **LDH, eosinophilia,** pan-**cytopenia, neutropenia.**

Several cephalosporins have been **implicated in triggering seizures, particularly** in patients with **renal** impairment, when the **dosage was** not reduced **(see** DOSAGE AND **ADMINISTRATION** and **OVERDOSAGE).** If **seizures associated with drug** therapy **occur,** the drug **should** be **discontinued. Anticonvulsant therapy** can be given **if clinically** indicated.

OVERDOSAGE

A study of children under six years of age suggested that ingestion of **less than** 250 **mg/kg** of **cephalosporins** is not **associated with significant outcomes. No** action **is** required other than general support and observation. For amounts **greater than 250 mg/kg,** induce gastric emptying.

In five **anuric** patients, it **was** demonstrated that an average **of 63% of a 1 g oral dose is extracted from the body during a** 6–8 hour **hemodialysis** session.

DOSAGE AND ADMINISTRATION

DURICEF **is** acid-stable and may be **administered** orally **without regard to** meals. Administration with **food** may be **helpful** in **diminishing potential gastrointestinal complaints** occasionally associated **with oral cephalosporin therapy.**

Adults

Urinary Tract Infections: For uncomplicated lower urinary tract infections (i.e., cystitis) **the** usual **dosage is** 1 or2 **g** per day in **single (q.d.)** or divided doses **(b.i.d.).**

For **all other** urinary **tract infections the usual dosage** is 2 g per day in divided doses **(b.i.d.).**

Skin and Skin Structure Infections: For **skin and** skin structure infections **the usual dosage is 1 g per day in single** (q.d.) or divided **doses (b.i.d.).**

Pharyngitis and Tonsillitis: Treatment Of group A beta-hemolytic **streptococcal pharyngitis and tonsillitis —1 g per** day in **single (q.d.)** or **divided doses (b.i.d.) for 10 days.**

Children

For urinary **tract** infectious, the **recommended** daily **dosage** for children **is 30** m&g/day in divided doses every 12 hours. For **pharyngitis, tonsillitis,** and impetigo, the recommended daily dosage for children is 30 **mg/kg/day** in **a single dose** or in equally divided doses every 12 hours. For other **skin** and kin structure infections, the **recommended** daily dosage is **30 mg/kg/day** in **equally** divided doses every 12 **hours.** In the treatment of **beta-hemolytic streptococcal infections,** a **therapeutic** dosage of DURICEF should be **administered** for at east 10 days.

See **chart** for **total** daily dosage for **children.**

DAILY DOSAGE OF **DURICEF®** SUSPENSION,

Child's Weight				
lbs	kg	125 mg/ 5 mL	250 mg/ 5 mL	500 mg/ 5 mL
L0	4.5	1 tsp	—	
30	9.1	2 tsp	1 tsp	
30	13.6	3 tsp	1% tsp	
40	18.2	4 tsp	2 tsp	1 tsp
50	22.7	5 tsp	2½ tsp	1% tsp
60	27.3	6 tsp	3 tsp	1½ tsp
70 & above	31.8+	—	—	2 tsp

In patients with renal impairment, the dosage of cefadroxil monohydrate should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1000 mg of DURICEF (cefadroxil monohydrate, USP) and the maintenance dose (based on the creatinine clearance rate [mL/min/1.73 M²]) is 500 mg at the time intervals listed below.

Creatinine Clearances	Dosage Interval
O-10 mL/min	36 hours
Io-25 mL/min	24 hours
25–50 mL/min	12 hours

Patients with creatinine clearance rates over 50 mL/min may be treated as if they were patients having normal renal function.

Reconstitution Directions for Oral Suspension

Bottle Size	Reconstitution Directions
100 mL	Suspend in a **total** of 67 **mL** water. **Method:** Tap **bottle** light **to** loosen powder. Add 67 **mL** of water in two p&ions. Shake **well** after **each addition.**
75 mL	**Suspend** in **a total** of **51 mL water. Method: Tap bottle light to loosen** powder. Add 51 **mL of water** in two portions. **Shake well after** each addition.
50 mL	Suspend **in a** total of 34 **mL** water **Method:** Tap **bottle lightly to loosen** powder. Add 34 **mL** of water in **two portions.** shake **well after each addition.**

After reconstitution, store in refrigerator. Shake well before using. Keep container tightly closed. Discard unused portion after 14 days.

HOW SUPPLIED

DURICEF® (cefadroxil monohydrate, USP) 500 mg Cap sules: opaque, in&i+& **and** white hard **gelatin capsules, imprinted** with' **"PPP" and** "784' on **one** end and with **"DURICEF"** and **"500 mg" on the other** end. **Capsules are** supplied **as follows:**

NDC 0087-0784-07	Bottle of 20
NDC 0087-0784-46	Bottle of 50
NDC 0087-0784-42	Bottle of 100
NDC 0087-0784-44	10 strips of 10 individually labeled blisters with 1 capsule per blister

Store at controlled room **temperature (15°–30°C).**

DURICEF® 1 **gram Tablets:** white **to off white, top** bii oval shaped, imprinted with **"PPP" on one side of the** bii **and "785"** on the other side **of the bisect. Tablets are supplied as follows:**

NDC 0087-0785-43	Bottle of 50
NDC 0087-0785-42	Bottle of 100
NDC 0087-0785-44	10 strips of 10 individually labeled blisters with 1 tablet per blister

Store at controlled room temperature (15°–30°C).

DURICEF® for Oral Suspension is orange-pineapple flavored, and is supplied as follows:

125 mg/5 mL	NDC 0087-0786-42	50 mL Bottle
	NDC 0087-0786-41	100 mL Bottle
250 mg/5 mL	NDC 0087-0782-42	50 mL Bottle
	NDC 0087-0782-41	100 mL Bottle
500 mg/5 mL	NDC 0087-0783-42	50 mL Bottle
	NDC 0087-0783-05	75 mL Bottle
	NDC 0087-0783-41	100 mL Bottle

Prior to reconstitution: Store at **controlled room temperature (15°–30°C).**

REFERENCES

1. National Committee for Clinical Laboratory Standards, Approved Standard, *Performance Standards for Antimicrobial Disk Susceptibility Test, 4th Edition,* Vol. 10 (7): M2-A4, Villanova, PA, April, 1990. 2. National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically,* 2nd Edition, Vol. 10 (8): M7-A2, Villanova, PA, April, 1990.

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Bristol-Myers Squibb Company
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USA

Shown in Product Identification Guide, page 308

ESTRACE® Rx
(es'trās)
ESTRADIOL VAGINAL CREAM, **USP, 0.01%**

Rx only

WARNINGS

1. **ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POST-MENOPAUSAL WOMEN.**
Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.
2. **ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.**
There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.
Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other